applications. Claims 7, 24, and 25 have been amended in order to recite more clearly the invention as taught in the specification. In particular, claim 7 has been amended to reflect Applicant's election of the peptide of SEQ ID NO.:1. Claims 24 and 25 have been amended to delete their dependencies from canceled claims and to correct a typographical error in claim 25.

1. ABSTRACT

The Examiner remarked in the Office Action of February 15, 2002 that the application does not contain an abstract of the disclosure as required by 37 C.F.R. § 1.72 (b). In response Applicant's have shortened the Abstract to not exceed 150 words as required by 37 C.F.R. § 1.72 (b).

2. CLAIM OBJECTIONS

The claims have been amended to reflect Applicant's election in response to the Office Action of October 2, 2001 as discussed above. Claim 25 has been amended to correct the misspelling of interleukin-4 as noted by the Examiner.

3. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 7, 24, and 25 are rejected under 35 U.S.C. § 112, first paragraph, allegedly, since the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention. The Examiner alleges that "[t]he disclosure fails to provide adequate guidance pertaining to a number of [...] considerations [...]" that "[...] govern enablement determinations pertaining to undue experimentation [...]" as set forth in *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988) and *Ex parte Forman*, 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986).

Applicants respectfully disagree. Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *Fields v. Conover*, 170 U.S.P.Q. 276, 279 (C.C.P.A. 1971). The factors that can be considered in determining whether an amount of experimentation is undue have been listed in *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the amount of effort involved, the guidance provided by the specification, the presence of working examples, the amount of pertinent literature and the level of skill in the art. The test for

undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. *Id.*

While the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of the experiment is not a consideration. Indeed, the Court of Custom and Patent Appeals has specifically cautioned that the unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue in *In re Angstadt*, 190 U.S.P.Q. 214 (C.C.P.A. 1976):

> [If to fulfill the requirements of 112, first paragraph, an applicant's] disclosure must provide guidance which will enable one skilled in the art to determine, with reasonable certainty before performing the reaction whether the claimed product will be obtained, . . . then all "experimentation" is "undue" since the term "experimentation" implies that the success of the particular activity is uncertain. Such a proposition is contrary to the basic policy of the Patent Act. *Id.* at 219 (emphasis in the original).

Applicants respectfully submit that it is not undue experimentation to produce the peptides of the present invention and to determine whether the produced peptide is effective in increasing the production of at least one Th1 cytokine or in decreasing the production of at least one Th2 cytokine.

Further, under 35 U.S.C. § 112, patent applicants' specification which contains a teaching of how to make and use the invention must be taken as enabling unless the Patent and Trademark Office provides sufficient reason to doubt the accuracy of the disclosure. *In re Marzocchi*, 439 F.2d 220, 223-24, 169 U.S.P.Q. 367, 369-70 (CCPA 1971). The claimed invention disclosed in the specification cannot be questioned on the unsupported skepticism of the Examiner. *Ex parte Linn*, 123 U.S.P.Q. 262 (PTO Bd. Pt. App. Int. 1959); *Ex parte Rosenwald*, 123 U.S.P.Q. 261 (PTO Bd. Pt. App. Int. 1959) (emphasis added). The number and variety of examples is irrelevant if the disclosure is "enabling" and set forth the "best mode contemplated." There is no absolute statutory requirement for a working example if the disclosure is such that one skilled in the art can practice the claimed invention. *In re Borkowski et al.*, 164 U.S.P.Q. 642 (CCPA 1970) (emphasis added). Even in an unpredictable art, Section 112 does not require disclosure of a test of every species encompassed by the claims. *In re Angstadt*, 190 U.S.P.Q. 214, 218 (CCPA 1976). An

invention is enabled even though the disclosure may require some routine experimentation to practice the invention. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). The fact that the required experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *M.I.T. v A.B. Fortia*, 774 F.2d 1104, 227 U.S.P.Q. 428 (Fed. Cir. 1985). A considerable amount of experimentation is permitted if it is merely routine or the specification provides a reasonable amount of guidance and direction to the experimentation. *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988); *In re Jackson*, 217 USPQ 804, 807 (PTO Bd. Pt. App. Int. 1982) (emphasis added). Finally, the Examiner has the burden of showing that the disclosure entails undue experimentation. *In re Angstadt*, 537 F.2d 498, 190 U.S.P.Q. 214 (CCPA 1976) (emphasis added).

Here, the specification provides considerable guidance and direction to practice the claimed invention. In particular, the application provides ample guidance as to how to make the peptides (see, *e.g.*, section 4.1.) and how to administer, *i.e.*, use the peptides (see, *e.g.*, page 20, line 15 to page 24, line 28).

An invention meets the standard for successful practice set by Section 112 unless the invention is "totally incapable of achieving a useful result." *Brooktree v. Advances Micro Devices*, 24 U.S.P.Q.2D 1401, 1412 (Fed. Cir. 1992). The Examiner's attention is directed to the opinion of the Court of Appeals for the Federal Circuit (Federal Circuit) in *In re Brana*, 34 U.S.P.Q.2d 1437 (Fed. Cir. 1995). In *Brana*, the Board had affirmed a final rejection under Section 112, 1st paragraph, of claims covering certain compounds asserted to be useful as anti-tumor substances because it was alleged that the specification was non-enabling since it did not sufficiently establish that the claimed compounds had a practical utility, *i.e.*, as anti-tumor agents. 34 U.S.P.Q.2d at 1439.

The Federal Circuit emphatically reversed the Board's decision. First, it explained the legal standard for compliance with the relevant Section 112 requirement, explaining that "unless there is reason to doubt the objective truth of the statements contained [in the specification] which must be relied on for enabling support", a specification's disclosure "must be taken as in compliance with the enabling requirement." *Id.* at 1441 (emphasis in the original). Further, the *Brana* Court made clear that the Patent and Trademark Office has the initial burden of challenging a presumptively correct assertion of

utility; evidence must be presented that those of skill in the art would doubt the disclosure. Only then must applicants provide rebuttal evidence.

Second, the Federal Circuit explained that even if one of skill in the art would have questioned the asserted utility, all applicants need do to overcome the rejection is to proffer sufficient evidence to convince one skilled in the art of the asserted utility. *Id.* at 1441.

In view of the knowledge in the art and the teachings in the specification, Applicants submit that one of skill in the art can practice the claimed invention without undue experimentation.

The Examiner contends that "[t]he disclosure fails to provide adequate guidance pertaining to the molecular determinants modulating the favorable immunological properties and activities of the claimed peptide[s]". The Examiner further notes that "[...] it is not readily manifest how the administration of this peptide will modulate the immune response[...]". In response, Applicants respectfully point out that these contentions relate to the mechanism of action of the claimed peptides. However, knowledge of the underlying mechanism is not required to make and use the peptides recited in the claims. Further, there is no legal requirement, that the mechanism of action of an invention be disclosed in a patent application.

The Examiner further contends that "[t]he disclosure fails to teach that modulating T_H1/T_H2 cytokine levels will have any ameliorative or therapeutic effect in cardiovascular disease, allergic disorders, solid tumors, or the progression to AIDS". The Examiner also contends that "the complexity of the TCR and the various roles it plays in T-cell signaling make it difficult to identify and predict which compounds will prove useful as therapeutic agents". In response, Applicants respectfully point out that the enablement requirement of 37 C.F.R. § 112 pertains to the claimed invention. See MPEP § 2164: "The invention that one skilled in the art must be enabled to make and use is that defined by the claim(s) of the particular application or patent." The currently pending claims recite methods for increased production of at least one Th1 cytokine or to decrease the production of at least one Th2 cytokine. The ameliorative or therapeutic effects mentioned by the Examiner relate to the utility of the invention and should be evaluated by the utility guidelines. Thus, the Examiner's contention of lack of predictability regarding the therapeutic uses put forth for the invention is an allegation of lack of utility. The Utility Guidelines (M.P.E.P. 2107) are

applicable when there is an allegation of lack of utility under § 112. Under the Utility Guidelines, evidence of utility is sufficient if it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. There is no requirement to provide data from human clinical trials for establishing utility of an invention related to treatment of human disease. All that is required is a reasonable correlation between the effectiveness of the methods and the asserted use. (See Utility Guidelines, M.P.E.P. 2107.03(I)). Such a correlation is clearly available for the presently claimed invention.

The Examiner further contends that no working embodiments are provided. In response, Applicants respectfully point out that, as discussed above, there is no statutory requirement for such working examples.

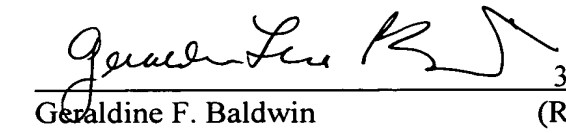
The Examiner also contends that the scope of the claims is to broad as "[t]he claims encompass the treatment of any solid tumor, any cardiovascular disorder, any allergic disorder, and the progression to AIDS." In response, Applicants respectfully point out that the currently pending claims are directed to methods for increasing the production of at least one Th1 cytokine or to decrease the production of at least one Th2 cytokine and that the treatments listed by the Examiner relate to the utility of the claimed method. As discussed above, the applicable standard for utility is different from the standard for enablement. Thus, the Examiner's argument is mute with regard to the enablement of the claimed invention of the present application.

In view of the above amendments and remarks, it is submitted that the specification provides sufficient teaching to allow one skilled in the art to successfully make and use the claimed methods for increasing the production of at least one Th1 cytokine or to decrease the production of at least one Th2 cytokine, without undue experimentation. The rejection under Section 112, first paragraph, therefore, should be withdrawn.

Applicants respectfully request that the above-made remarks be made of record in the file history of the present application.

Respectfully submitted,

Date: August 15, 2002



31,232
Geraldine F. Baldwin (Reg. No.)

PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, New York 10036-2711
(212) 790-9090

EXHIBIT A
CLAIM AMENDMENTS WITH MARKINGS

Matter that has been deleted from claims is indicated by brackets and matter that has been added is indicated by underlining.

7. (Amended) A method to increase production of at least one Th1 cytokine or to decrease production of at least one Th2 cytokine in an individual free of infection with an immunodeficiency-type retrovirus comprising administering an effective amount of a peptide selected from the group consisting of peptides comprising the amino acid sequence Cys Lys Pro Ile Ser Gly His Asn Ser Leu Phe Trp Tyr Arg Gln Thr (SEQ ID NO:1), [Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Arg Leu Thr Val Val (SEQ ID NO:2), Leu Lys Ile Gln Pro Ser Glu Pro Arg Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:3), Leu Thr Ile Gln Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:4), Leu Ile Leu Glu Ser Ala Ser Thr Asn Gln Thr Ser Met Tyr Leu Cys Ala (SEQ ID NO:5), Leu Thr Val Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser (SEQ ID NO:6), Leu Ala Ile Ser Gly Leu Glu Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala (SEQ ID NO:7), Phe Thr Ile Ser Gly Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:8), Leu Thr Ile Ser Gly Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln (SEQ ID NO:9), Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser (SEQ ID NO:10) and Leu Thr Ile Asn Pro Val Glu Ala Asp Asp Val Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:11), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Lys Leu Thr Val Val (SEQ ID NO:12), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Glu Leu Thr Val Val (SEQ ID NO:13), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Asp Leu Thr Val Val (SEQ ID NO:14), and Thr Phe Gly Xaa Gly Thr Yaa, wherein Xaa is any amino acid and Yaa is Arg, Lys, Asp, Glu, His or other charged amino acid molecule (SEQ ID NO:15),] or a derivative thereof, to an individual free of infection with an immunodeficiency-type retrovirus in an amount sufficient to increase production of at least one Th1 cytokine or decrease production of at least one Th2 cytokine.

24. (Amended) The method according to claim [6 or] 7 in which the Th1 cytokine is selected from the group consisting of interleukin 2 and interferon-γ.

25. (Amended) The method according to claim [6 or] 7 in which the Th2 cytokine is selected from the group consisting of [interleutkin-4,] interleukin-4, interleukin 5, interleukin 6, interleukin 10 and immunoglobulin G.

EXHIBIT B
PENDING CLAIMS
UPON ENTRY OF THE AMENDMENTS OF AUGUST 15, 2002
U.S. Patent Application No. 09/591,789 Atty. Docket No. 7760-012

WHAT IS CLAIMED IS

7. (Amended) A method to increase production of at least one Th1 cytokine or to decrease production of at least one Th2 cytokine in an individual free of infection with an immunodeficiency-type retrovirus comprising administering an effective amount of a peptide selected from the group consisting of peptides comprising the amino acid sequence Cys Lys Pro Ile Ser Gly His Asn Ser Leu Phe Trp Tyr Arg Gln Thr (SEQ ID NO:1), or a derivative thereof, to an individual free of infection with an immunodeficiency-type retrovirus in an amount sufficient to increase production of at least one Th1 cytokine or decrease production of at least one Th2 cytokine.

24. (Amended) The method according to claim 7 in which the Th1 cytokine is selected from the group consisting of interleukin 2 and interferon-γ.

25. (Amended) The method according to claim 7 in which the Th2 cytokine is selected from the group consisting of interleukin-4, interleukin 5, interleukin 6, interleukin 10 and immunoglobulin G.

EXHIBIT C
AMENDMENTS TO THE ABSTRACT WITH MARKINGS

Matter that has been deleted from the Abstract is indicated by brackets.

The present invention relates to methods for the prevention and/or treatment of cardiovascular and allergic diseases and disorders, methods for inhibiting the growth of, or reducing the volume of, a solid tumor, as well as methods for preventing progression to AIDS in an HIV-infected human, by administering a peptide derived from T cell receptors, or a derivative thereof. The present invention also relates to peptides derived from T-cell receptors, and derivatives thereof, which are useful in such methods. [The peptides are selected from the group consisting of Cys Lys Pro Ile Ser Gly His Asn Ser Leu Phe Trp Tyr Arg Gln Thr (SEQ ID NO:1), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Arg Leu Thr Val Val (SEQ ID NO:2), Leu Lys Ile Gln Pro Ser Glu Pro Arg Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:3), Leu Thr Ile Gln Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:4), Leu Ile Leu Glu Ser Ala Ser Thr Asn Gln Thr Ser Met Tyr Leu Cys Ala (SEQ ID NO:5), Leu Thr Val Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser (SEQ ID NO:6), Leu Ala Ile Ser Gly Leu Glu Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala (SEQ ID NO:7), Phe Thr Ile Ser Gly Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:8), Leu Thr Ile Ser Gly Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln (SEQ ID NO:9), Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser (SEQ ID NO:10) and Leu Thr Ile Asn Pro Val Glu Ala Asp Asp Val Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:11), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Lys Leu Thr Val Val (SEQ ID NO:12), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Glu Leu Thr Val Val (SEQ ID NO:13), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Asp Leu Thr Val Val (SEQ ID NO:14), Thr Phe Gly Xaa Gly Thr Yaa, wherein Xaa is any amino acid and Yaa is Arg, Lys, Asp, Glu, His or other charged amino acid molecule (SEQ ID NO:15), or a derivative thereof.]

EXHIBIT D
ABSTRACT
U.S. Patent Application No. 09/591,789 Atty. Docket No. 7760-012

The present invention relates to methods for the prevention and/or treatment of cardiovascular and allergic diseases and disorders, methods for inhibiting the growth of, or reducing the volume of, a solid tumor, as well as methods for preventing progression to AIDS in an HIV-infected human, by administering a peptide derived from T cell receptors, or a derivative thereof. The present invention also relates to peptides derived from T-cell receptors, and derivatives thereof, which are useful in such methods.